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Synthesis of embellished bicyclo[2.2.2]octenones and a sigmatropic 1,2-acyl shift in an excited state: a novel and stereoselective route to (±)-hirsutic acid C and complicatic acid

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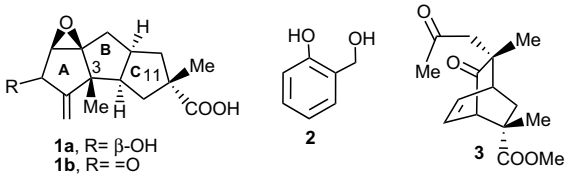
This paper is dedicated to Professor Goverdhan Mehta, an inspiring teacher and mentor, on the occasion of his 60th birthday

Abstract—Formal syntheses of hirsutic acid C and complicatic acid via cycloaddition of cyclohexa-2,4-dienone with methyl methacrylate and a triplet sensitized 1,2-acyl shift are described. The X-ray crystal structure of one of the key intermediates is also reported.

The efficient creation of molecular complexity, atom economy, and stereoselectivity are some of the important criteria in the design and development of new synthetic methods.[1–3] Cascades of reactions[2d,f] or reactions in tandem[2c,e,3] and multi-component reactions[4] are often employed to achieve this objective. There has been an intense interest in the synthesis of polyquinane natural products and a plethora of methods have been developed.[5] The search for new methods involving rapid generation of structural and functional complexity is continuing.[6,7] Hirsutic acid **1a** is an important member of the hirsutane family of polyquinane natural products that was isolated from *Stereum hirsutum* and *Stereum complicatum* along with a closely related compound complicatic acid **1b** that exhibits interesting biological properties.[8] Unlike other members of this family, only a few syntheses of hirsutic acid have been reported.[5,9] However, a majority of these generate the *cis:anti:cis* triquinane framework only after a multi-step sequence. Moreover, except in a couple of cases, the angular methyl group at C-3 and the quaternary carbon at C-11 having methyl and carboxyl groups were introduced during the later stages of the syntheses, often in a non-stereoselective manner. In view of the above, we developed a new method for the rapid generation of molecular complexity from simple aromatic precursors that involves cycloaddition of cyclohexa-2,4-dienones with various types of π-systems.[10] We wish to report herein a short and stereoselective formal synthesis of hirsutic acid C **1a** and complicatic acid **1b** from salicyl alcohol **2** that involves synthesis of the functionalized and appended bicyclo[2.2.2]octenone **3** and a sigmatropic 1,2-acyl shift (or oxa-di-π-methane rearrangement) in the triplet excited state (Fig. 1).

Our strategy is based on the recognition of the structural, functional, and stereochemical features of **1**, and the key tricyclic intermediate **5**, which has already been converted to **1a**,**b**, with those of the bicyclo[2.2.2]octenone **3** (Scheme 1). It was contemplated that a photochemical 1,2-acyl shift in **3** would readily give the diquinane **4** that, after peripheral cleavage of the



1a, R= β-OH
1b, R= =O

2

3

Figure 1.

Keywords: Cycloaddition; Oxa-di-π-methane rearrangement; 1,2-Acyl shift; Hirsutic acid; Complicatic acid.

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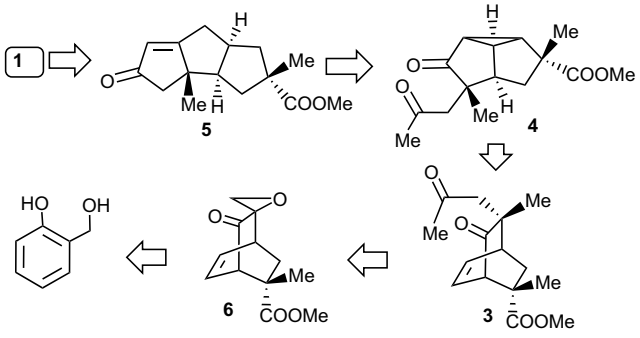


Scheme 1.

cyclopropane ring and subsequent aldol condensation, would provide the desired triquinane **5**. Further, it was thought that the embellished bicyclic precursor **3** would be derived from the keto-epoxy ester **6** by manipulation of the oxirane ring, the ketoester **6** being obtained from salicyl alcohol.

There are several noteworthy features of our strategy. For example, all the 14 carbons of the triquinane intermediate **5**, hirsutic acid and complicatic acid are present in the key precursor **3**, which is derived from salicyl alcohol and methyl methacrylate. Remarkably, all the three five-membered rings and all the four stereogenic centers required in **5** are present in the ketoester **3** in latent form. In addition, the β,γ-enone chromophore that is required for the key structural reorganization (**3** → **4**) in the excited state at later stages, is also generated at the beginning of the route.

Conceptually, the desired bicyclo[2.2.2]octenone **3** may be available via cycloaddition of cyclohexadienone **7** with methyl methacrylate (Fig. 2). However, while 6-acetoxycyclohexadienones are available through oxidation of substituted phenols,[11] there are only a few methods[12] for the preparation of 6,6-dialkylcyclohexa-2,4-dienones, which appeared to be unsuitable for our purpose. Hence, an indirect route to **3** and congeners was developed from the ketoepoxide **6** as presented below.

Salicyl alcohol was oxidized with sodium *meta*-periodate to give the epoxydimer **9a**,[13a] which was readily converted into the chlorohydroxy derivative **9b**.[13] Generation of **8** by pyrolysis of **9b** and subsequent interception with methyl methacrylate following an earlier procedure[10b] gave the adduct **10** in excellent yield (85%) along with a small amount of the *exo* adduct. Treatment of the adduct **10** with KOH in $CHCl_3$–H_2O containing CTAB as a phase transfer catalyst gave the epoxy ketone **6** in quantitative yield. The structure of ketoepoxide **6** was clearly suggested by its spectral data[†] and confirmed through further transformation. Treatment of the adduct **6** with zinc in dry dioxane containing ammonium chloride furnished the ketone **11** (*syn:anti* mixture) as a result of deoxygenation of the oxirane ring. Subsequent alkylation of **11** with allyl bromide in the presence of sodium hydride in tetrahydrofuran followed by chromatography of the crude product gave the allylated derivative **12** as a result of stereoselective alkylation from the π face (Scheme 2). The structure and stereochemistry of the alkylated product **12** were deduced from the spectral data and further transformation into **4** (vide infra).

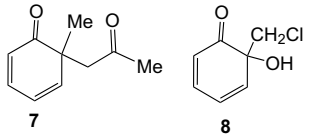


Figure 2.

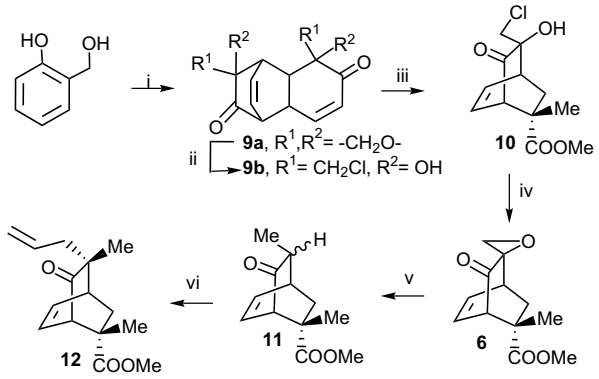
Wacker oxidation[14] of the bicyclic precursor **12** gave the desired ketone **3** having all the requisite appendages and functional groups for further elaboration (Scheme 3). Both the bicyclic compounds **12** and **3** containing a β,γ-enone chromophore were transformed into the diquinane intermediate **4** by triplet sensitized photochemical reactions. In general, rigid β,γ-enones undergo two unique reactions that are characteristic of their excited states. The triplet sensitized irradiation leads to a 1,2-acyl shift (or oxa-di-π-methane rearrangement) and singlet excitation induces a 1,3-acyl shift.[15,16] However, the photoreactivity depends on the structure of the chromophoric system and functional group in a subtle fashion. Keeping in mind the structural and functional complexity of our chromophoric systems, first a solution of **12** in acetone (solvent as well as sensitizer) was irradiated with a mercury vapor lamp (APP, 125 W) for

[†] All the compounds were thoroughly characterized with the help of spectroscopic and analytical data. Selected data for compound **6**: mp 68–70 °C. IR (film) ν_{max}: 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.53 (dd, $J_1, J_2 = 7$ Hz, 1H), 6.26 (dd, $J_1, J_2 = 7$ Hz, 1H), 3.67 (s, 3H), 3.46 (d, $J = 5.7$ Hz, 1H) 3.15 (part of AB system, $J = 6$ Hz, 1H), 2.81 (part of AB system, $J = 6.1$ Hz, 1H), 2.48 (m, 2H), 1.90 (d, $J = 12.3$ Hz, 1H), 1.34 (s, 3H). ^{13}C NMR (75 MHz): δ 203.25, 175.45, 135.08, 129.54, 57.21, 56.16, 52.98, 52.42, 46.78, 38.08, 33.97, 25.91. Mass (*m*/*z*): 222 (M^+).

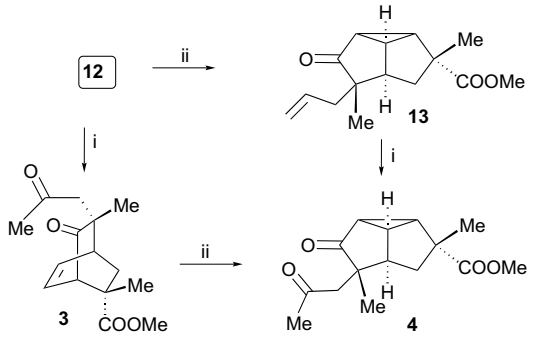
Compound **4**: mp 104–106 °C. IR (film) ν_{max}: 1726, 1703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.72 (s, 3H, OCH_3), 3.13 (m, 1H), 2.78 (m, 1H), 2.60–2.44 (m, 4H), 2.13 (s, 3H), 1.95 (dd, $J_1 = 5.1$ Hz, $J_2 = 9.9$ Hz, 1H), 1.75 (d, $J = 14.4$ Hz, 1H), 1.24 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (75 MHz): δ 217.4, 206.0, 177.4, 56.1, 52.3, 51.6, 51.2, 47.2, 43.0, 42.2, 36.4, 34.5, 32.0, 23.0, 16.7. Mass (*m*/*z*): 264 (M^+).

Crystal data: $C_{15}H_{20}O_4$, M 264.13, space group, monoclinic, *P*21/*c*, $a = 5.997(8)$, $b = 11.3480(9)$, $c = 21.2510(16)$ Å, $\lambda = 0.70903$ Å, $\alpha = 90.000(6)$, $\beta = 97.327(8)$, $\gamma = 90.000(8)°$, $U = 1434.4(2)$ $Å^3$, $Z = 4$, $D_c = 1.224$ mg/m^3, $T = 293(2)$ K, $F(000) = 568$, size = $0.4 \times 0.15 \times 0.10$ mm. Reflections/collected/unique 1996/1996 [*R*(int) = 0.0000], final *R* indices [$I > 2$sigma(I)] = $R_1 = 0.0508$, $wR_2 = 0.1111$], *R* indices (all data) $R_1 = 0.0784$, $wR_2 = 0.1272$. CCDC no 226012, see http://www.ccdc.cam.ac.uk/conts/retrieving.html (e-mail: deposit@ccdc.cam.ac.uk).

Compound **5**: IR (film) ν_{max}: 1727, 1709 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ, 5.65 (s, 1H), 3.65 (s, 3H), 2.83–2.63 (m, 2H), 2.52 (dd, $J_1 = 12$ Hz, $J_2 = 6.5$ Hz, 1H), 2.44–2.28 (m, 3H), 2.24 (s, 2H), 1.50–1.39 (m, 1H), 1.34 (s, 3H), 1.24 (t, $J = 11.6$ Hz, 1H), 1.11 (s, 3H). ^{13}C NMR (75 MHz): δ 208.98, 193.65, 177.28, 122.66, 54.71, 52.52, 51.96, 50.78, 49.13, 46.44, 44.53, 37.26, 32.57, 24.69, 24.53. HRMS: found 248.1425 (M^+), $C_{15}H_{20}O_3$ requires 248.1412.



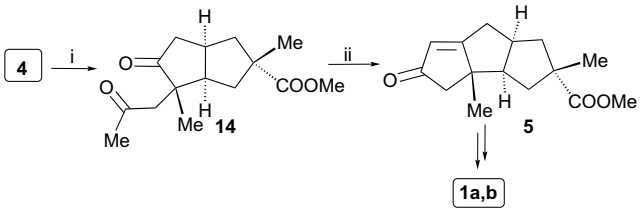
Scheme 2. Reagents and conditions: (i) aq $NaIO_4$, 90%; (ii) HCl, dioxane, 90%; (iii) *o*-dichlorobenzene, methyl methacrylate, 85%; (iv) KOH, $CHCl_3$–H_2O, CTAB, quantitative; (v) Zn, NH_4Cl, dry dioxane, Δ, 68%; (vi) NaH–THF, allyl bromide, 65%.



Scheme 3. Reagents and conditions: (i) $PdCl_2$, CuCl, O_2, aq DMF (12 h for **12** to **3**, 75%; 24 h for **13** to **4**, 68%); (ii) *hν*, acetone (3.5 h for **12** to **13**, 30%; 1.5 h for **3** to **4**, 42%).

3.5 h under nitrogen. Chromatography of the photolysate yielded the photoproduct **13** in 30% yield along with some recovered starting material. Oxidation of **13** with $PdCl_2$ readily gave the diquinane **4**. It appeared that the low efficiency of the 1,2-acyl shift (or oxa-di-π-methane rearrangement) in the above photoreaction could be due to competitive absorption of light by the olefinic group present in the allylic chain.

Irradiation of a solution of **3** in dry acetone (sensitizer and solvent) under nitrogen gave the diquinane **4** in good yield (42%) (Scheme 3). Though, the structure of the diquinane **4** was evident from its spectral data, its



Scheme 4. Reagents and conditions: (i) $(Bu)_3SnH$, AIBN, benzene, Δ, 60%; (ii) KO^{t}Bu–^{t}BuOH, 15 min, 70%.

stereochemistry was confirmed by X-ray crystallography (Fig. 3). Thus, the structures and stereochemistry of the preceding intermediates were also established.

Towards synthesis of the intermediate **5**, the peripheral cyclopropane bond in the diquinane **4** was selectively cleaved by treatment with tributyltin hydride-AIBN[17] in refluxing benzene to give **14** in good yield (60%). An aldol condensation in **14** readily gave the linearly fused tricyclopentanoid **5** (Scheme 4), which has already been elaborated to hirsutic acid[9c–f] and complicatic acid.[9d] The structure of the triquinane **5** was deduced from its spectral data,[†] which were in good agreement with those reported in the literature.[9c,d,f] Thus, a formal syntheses of hirsutic acid and complicatic acid was complete.

In summary, we describe an efficient and novel route to hirsutic acid and complicatic acid from the bicyclic intermediate **3** derived from salicyl alcohol and methyl methacrylate. The methodology involved cycloaddition between two electron deficient partners, a stereoselective π-facial alkylation and a photochemical 1,2-acyl shift as key features. In addition to the brevity, stereoselectivity, and rapid generation of molecular complexity, the simplicity of the reagents and conditions are noteworthy features of this methodology.

Acknowledgements

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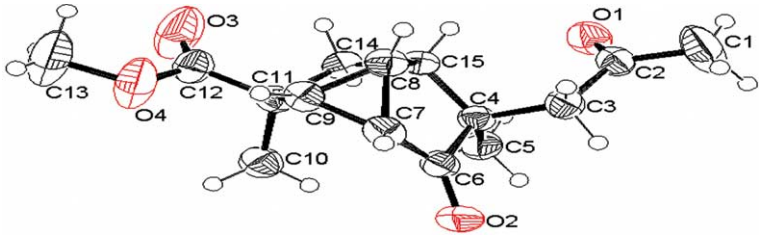

Figure 3. X-ray crystal structure of compound **4**.

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